Remarks

The Applicants have amended the Specification to place it into final condition for allowance.

Claim 11 has been amended to remove one of the four Q moieties and the associated moieties associated with the removed Q moiety. Claim 11 has further been amended to recite that the nausea and vomiting that is being treated is caused by a μ-opioid agonist compound. Support may be found in the Applicants' Specification on page 15 in the first full paragraph.

The Applicants have cancelled Claims 13, 15 and 17-22. Finally, the Applicants have amended Claim 16 to depend from Claim 11 in view of the cancellation of Claim 15. Entry of the above amendments into the Official File is respectfully requested.

Claims 15-16, 20 and 22 stand rejected under 35 U.S.C. §112, first paragraph. The Applicants respectfully submit that the rejection is now moot with respect to cancelled Claims 15, 20 and 22. The Applicants also respectfully submit that the rejection of Claim 16 is now moot in view of the change in dependency to Claim 11. Withdrawal of the rejection is respectfully requested.

Claims 1-22 stand rejected under 35 U.S.C. §103 over the combination of Choi and Rudd with Portoghese. The Applicants respectfully submit that the rejection is now moot with respect to cancelled Claims 13, 15 and 17-22. The Applicants nonetheless respectfully submit that one skilled in the art would not make the hypothetical combination and, in any event, such a hypothetical combination would still fail to result in the subject matter of the rejected claims. Details are set forth below.

The Applicants respectfully submit that Portoghese fails to disclose, teach or suggest a method of treating nausea and vomiting caused by a μ-opioid agonist compound. In fact, the Applicants have carefully reviewed the entire Portoghese disclosure and it fails to provide disclosure

with respect to treating nausea and emesis, irrespective of the cause such as the claimed μ-opioid agonist compound.

Thus, the rejection turns to Rudd and Choi to make up for such deficiencies. The problem is that both of the secondary and tertiary references fail to provide disclosure that would remedy the deficiencies of Portoghese.

With respect to Rudd, the rejection states:

> Rudd et al. teach naltrindole, naltrexone and naloxone (drugs having the same core structure of that of naltrindone (see enclosed attached structures) to inhibit the emetic reflex (vomiting) (see abstract and also page 82 (section 4.3 first para.) as in claims 20-22. Also note that the anti-emetic action of fentany [sic] is antagonized by the opioid receptor antagonist naltrxone [sic].

The Applicants respectfully submit that Rudd, irrespective of the characterizations set forth above in the rejection, fails to cure the deficiencies of Portoghese with respect to teaching methods of treating nausea and vomiting caused by a μ-opioid agonist compound as recited in the Applicants' claims.

First, it should be noted that the emesis of Rudd is induced by nicotine. The testing in Rudd is directed to determining the anti-emetic action of fentanyl to counteract the emesis induced by nicotine. That has nothing to do with the Applicants' claimed subject matter wherein the treatment of nausea and vomiting is caused by a μ-opioid agonist compound.

The second part of the teachings of Rudd is to whether opioid receptor antagonists such as naltrexone, naloxone and naltrindole antagonize fentanyl in the context of the inducement of emesis by nicotine. Rudd found that naltrexone, naloxone M8008 and MR2266 successfully antagonized the anti-emetic action of fentanyl. However, the Applicants respectfully submit that there is no disclosure in Rudd concerning the anti-emetic effect of naltrexone, naloxone and naltrindone on nicotine, which was the substance that induced emesis.

Moreover, Rudd discovered that a number of the opioid receptor antagonists did not antagonize the anti-emetic action of fentanyl. Those failed opioid receptor antagonists included naloxone methylbromide, naloxone methyliodide, naltrindole, DIPPA and naloxonazine. Thus, the Applicants respectfully submit that Rudd actually demonstrates that various of the known opioid receptor antagonists are not predictive of success in antagonizing fentanyl. Of course, this is far removed from whether such opioid receptor antagonists would be effective for treating nausea and vomiting caused by a μ-opioid agonist compound as claimed by the Applicants.

Thus, the compounds of Rudd as noted in the rejection, such as naltrindole, naltraxone and naloxone, are actually demonstrated to not be predictable in their effectiveness irrespective of any similarities in "core structure" as shown in the "e-molecules" attachment. In fact, careful scrutiny of that document (e-molecules) demonstrates that there are very significant chemical differences between those structures. For example, naltrindole has a five-membered nitrogen containing ring and a benzyl ring, which is nowhere to be found in both naltrexone and naloxone. Those skilled in the art are readily aware that such differences in chemical structure can provide radical differences in activity. In fact, the Applicants respectfully submit that Rudd demonstrates that fact. Therefore, the Applicants respectfully submit that any core structure similarity is inapplicable given the actual results discovered by Rudd that naltrindole was not effective to antagonize the anti-emetic action of fentanyl, while naltrexone and naloxone were.

In any event, the Rudd disclosure, as noted above, is directed to antagonization of the anti-emetic action of fentanyl by opioid receptor antagonists in the context of emesis inhibited by nicotine. This has nothing to do with the Applicants' rejected claims and nothing to do with Portoghese. The Applicants claim a method of treating nausea and vomiting caused by a μ-opioid agonist compound which is sharply different from nausea and vomiting caused by nicotine. Thus,

one skilled in the art would not combine Rudd with Portoghese and, even if one skilled in the art were to do so, the resulting teachings would still not result in the Applicants' claimed method of treating nausea and vomiting caused by a μ-opioid agonist compound.

The Applicants respectfully submit that the Choi disclosure does nothing to cure the deficiency set forth above with respect to both of Rudd and Portoghese. In that regard, Choi discloses:

> Small doses of the opioid antagonist naloxone administered intravenously maintain analgesia and reduce epidural morphine-induced side effects effectively.

The Applicants respectfully submit that the Choi disclosure does not cure the deficiencies of Rudd and Portoghese. The fact the naloxone, which is structurally completely different from the claimed compounds, can reduce epidural morphine-induced side effects fails to provide disclosure of treating nausea and vomiting caused by a μ-opioid agonist compound with the agents claimed by the Applicants. In that regard, both Rudd and the e-molecule article demonstrate that naloxone is structurally very, very different from other opioid antagonists and has completely different effects. Rudd demonstrated that while naloxone and naltrexone were successful in antagonizing the anti-emetic effect of fentanyl in an emetic situation induced by nicotine, they also found that naltrindole was unsuccessful. Moreover, Rudd found that various salts of naloxone were unsuccessful. What this means to those skilled in the art is that there is no reasonable expectation of success that the Choi disclosure with respect to naloxone could or would apply to the compounds of Portoghese or the Applicants. Thus, one skilled in the art would not make the hypothetical combination.

However, there is more. Dependence and physical tolerance tend to develop upon repeated administration of morphine, which is an opioid agonist (enclosed Reference 1, page 4, lines 4-5). However, it can be said that they have no relation to nausea and vomiting that can occur as adverse

reactions of morphine (Reference 1, page 8, lines 11-12). Thus, although Portoghese shows that naltrindole (NTI) is effective for treatment of dependence and tolerance, it does not mean that naltrindole (NTI) is effective for treatment of nausea and vomiting.

A variety of pharmacological actions may originate from opioid receptors and a particular action that actually develops depends on the type of the opioid receptors involved (enclosed Reference 2). For example, three types of agonists, μ, δ and κ, can work to develop analgesia. However, only the κ agonists have psychotomimetic and diuretic actions. As suggested by Portoghese, therefore, a μ agonist, for instance, can serve as an analgesic that is free of side effects such as psychotomimesis and diuresis that may be caused by other types of agonists such as κ. Thus, Portoghese does not at all disclose that naltrindole (NTI) can be effective for treatment of nausea or vomiting that occurs as a side effect of morphine.

Naltrexone and naloxone are μ antagonists which generally antagonize all actions of morphine, a μ agonist. Therefore, although they can control nausea and vomiting, ordinary systemic administration will retard the analgesic effects of morphine as well (enclosed Reference 3, page 1690, Fig. 2, left-lower) and cannot be effective in most cases for treatment of nausea and vomiting caused by morphine (Paragraph [0003] of the Applicants' Specification).

Choi discloses that when administered by a special procedure (epidural administration), naloxone can alleviate vomiting without reducing the analgesic effects of morphine. However, it is unknown whether similar results would be produced by systemic administration.

The Applicants respectfully submit that the claimed subject is non-obvious in discovering that the naltrindole (NTI) does not impair the analgesic effects of morphine (Reference 3, page 1690, Fig. 2, left-lower) and can be effective selectively for treatment of nausea and vomiting as shown in the Applicants' Specification, because it is selective for the δ, instead of μ, receptors (enclosed

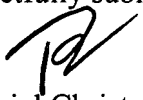
Reference 4).

There are complicated relationships between opioids, the μ agonist in particular, and emesis. A small dose of morphine can induce emesis while a large dose of morphine inhibits emesis (enclosed Reference 5, Abstract). The Applicants' claims are intended for treatment of such emesis caused by a small dose of morphine. Rudd focuses on the emesis-inhibiting action of fentanyl, which is a μ agonist, and studies the mechanism of its action to inhibit nicotine-induced nausea (identification of specific opioid receptor type involved) (Abstract, lines 1-3).

It is concluded that antagonism experiments with various opioid antagonists show that the anti-emetic action of fentanyl originates from $\mu 2$ receptors (Abstract, line 6). Some of the antagonism experiments use naltrindole as δ antagonist. Their results, however, only suggest that naltrindole has no influence on the anti-emetic effect of fentanyl and the are no findings on the effects on emesis induced by a small dose of μ agonists. Rudd also describes that a large dose of naloxone and naltrexone can induce emesis (Abstract, lines 7-8), and that fentanyl does not induce emesis when administered in doses used in the experiments for antagonism to the anti-emetic effect of fentanyl (page 82, section 4.3, paragraph 1, lines 3-4). Thus, Rudd is inapplicable, taken alone or with the other references. Withdrawal of the rejection is respectfully requested.

In light of the foregoing, the Applicants respectfully submit that the entire application is now in condition for allowance, which is respectfully requested.

Respectfully submitted,



T. Daniel Christenbury
Reg. No. 31,750
Attorney for Applicants

TDC/vbm
(215) 656-3381

PRESCRIBING INFORMATION

^{N}MS•IR®

Morphine Sulfate Immediate Release Tablets
5, 10, 20 and 30 mg

Purdue Pharma Std.
Opioid Analgesic
ATC: N02AA01

Purdue Pharma
575 Granite Court
Pickering, Ontario
L1W 3W8

Control No.: 100878

DATE OF PREPARATION:
September 17, 1990

DATE OF REVISION:
April 18, 2006

Reference 1

NAME OF DRUG

^{N}MS•IR®
Morphine Sulfate Immediate Release Tablets
5, 10, 20 and 30 mg

PHARMACOLOGICAL CLASSIFICATION

Opioid Analgesic

ACTIONS

Morphine is an opioid analgesic which exerts an agonist effect at specific, saturable opioid receptors in the CNS and other tissues. In man, morphine produces a variety of effects including analgesia, constipation from decreased gastrointestinal motility, suppression of the cough reflex, respiratory depression from reduced responsiveness of the respiratory centre to CO_2, nausea and vomiting via stimulation of the CTZ, changes in mood including euphoria and dysphoria, sedation, mental clouding, and alterations of the endocrine and autonomic nervous systems.

Morphine is readily absorbed when given orally, rectally or by s.c. or i.m. injection. Due to first-pass metabolism in the liver, the effect of an oral dose is less than after parenteral administration. With repeated regular dosing, oral morphine is about 1/3 as potent as when given by i.m. injection. Morphine is primarily excreted in the urine as morphine-3-glucuronide. About 7 to 10% of a dose of morphine is excreted in the feces via the bile.

INDICATIONS

For the symptomatic relief of severe pain.

CONTRAINDICATIONS

MS•IR® (morphine sulfate tablets) should not be given to patients with: hypersensitivity to opioid analgesics morphine or any other component of the product; in acute asthma or other obstructive airway disease and acute respiratory depression; cor pulmonale; cardiac arrhythmias; acute alcoholism; delirium tremens; severe CNS depression; convulsive disorders; increased cerebrospinal or intracranial pressure; head injury; brain tumor; suspected surgical abdomen; concomitant MAO inhibitors (or within 14 days of such therapy).

WARNINGS

Abuse of Opioid Formulations: MS•IR® (morphine sulfate tablets) is intended for oral use only. Abuse can lead to overdose and death. This risk is increased if MS•IR is taken with alcohol or other CNS depressants. With parenteral abuse, the tablet excipients, can be expected to result in local tissue necrosis, infection, pulmonary granulomas, and increased risk of endocarditis and valvular heart injury.

Patients should be instructed not to give MS•IR to anyone other than for whom it was prescribed, as such, inappropriate use may have severe medical consequences, including death.

Patients should be cautioned not to consume alcohol while taking MS•IR, as it may increase the chance of experiencing dangerous side effects.

MS•IR should be used with caution preoperatively and within the first 24 hours postoperatively.

Drug Dependence: As with other opioids, tolerance and physical dependence tend to develop upon repeated administration of morphine and there is potential for abuse of the drug and for development of strong psychological dependence. MS•IR should therefore be prescribed and handled with the high degree of caution appropriate to the use of a drug with strong abuse potential. Drug abuse is not usually a problem in patients with severe pain in which morphine is appropriately indicated. However, in the absence of a clear indication for a strong opioid analgesic, drug-seeking behaviour must be suspected and resisted, particularly in individuals with a history of, or propensity for drug abuse. Withdrawal symptoms may occur following abrupt discontinuation of morphine therapy or upon administration of a opioid antagonist. Therefore, patients on prolonged therapy should be withdrawn gradually from the drug if it is no longer required for pain control.

CNS Depression: Morphine should be used only with caution and in reduced dosage during concomitant administration of other opioid analgesics, general anaesthetics, phenothiazines and other tranquilizers, sedative-hypnotics, tricyclic antidepressants and other CNS depressants (including alcohol). Respiratory depression, hypotension and profound sedation or coma may result.

Severe pain antagonizes the subjective and respiratory depressant actions of morphine. Should pain suddenly subside, these effects may rapidly become manifest. Patients who are scheduled for cordotomy or other interruption of pain transmission pathways should not receive **MS•IR** within 24 hours of the procedure.

Use in Pregnancy: Animal studies with morphine and other opioids have indicated the possibility of teratogenic effect. In humans, it is not known whether morphine can cause fetal harm when administered during pregnancy or can affect reproductive capacity. **MS•IR** should be given to pregnant patients only if clearly needed and when the anticipated benefits outweigh the risks to the fetus.

PRECAUTIONS

Respiratory Depression: Morphine should be used with extreme caution in patients with substantially decreased respiratory reserve, pre-existing respiratory depression, hypoxia or hypercapnia. Such patients are often less sensitive to the stimulatory effects of carbon dioxide on the respiratory center and the respiratory depressant effects of morphine may reduce respiratory drive to the point of apnea.

Head Injury: The respiratory depressant effects of morphine, and the capacity to elevate cerebrospinal fluid pressure, may be greatly increased in the presence of an already elevated intracranial pressure produced by trauma. Also, morphine may produce confusion, miosis,

vomiting and other side effects which obscure the clinical course of patients with head injury. In such patients, morphine must be used with extreme caution and only if it is judged essential.

Hypotension: Morphine administration may result in severe hypotension in patients whose ability to maintain adequate blood pressure is compromised by reduced blood volume, or concurrent administration of such drugs as phenothiazines or certain anaesthetics.

Acute Abdominal Conditions: Morphine has been shown to decrease bowel motility. Morphine may obscure the diagnosis or clinical course of patients with acute abdominal conditions.

Special Risk Groups: Morphine should be administered with caution, and in reduced dosages, to elderly or debilitated patients, to patients with severely reduced hepatic or renal function, and to patients with adrenocortical insufficiency (e.g., Addison's disease), biliary tract disorders, hypothyroidism, pancreatitis, prostatic hypertrophy or urethral stricture.

Morphine should not be used where there is the possibility of paralytic ileus occurring.

Morphine may lower the seizure threshold in patients with a history of epilepsy.

Use during Labor/Delivery and in Nursing Mothers: Morphine crosses the placental barrier and its administration during labor can produce respiratory depression in the neonate. Morphine has

been detected in human breast milk. Caution should be exercised if morphine is administered to a nursing mother.

Driving and Operating Dangerous Machinery: Morphine may impair the mental and/or physical abilities needed for certain potentially hazardous activities such as driving a car or operating machinery. Patients should be cautioned accordingly.

Patients should also be cautioned about the combined effects of morphine with other CNS depressants, including other opioids, phenothiazines, sedative/hypnotics and alcohol.

Drug Interactions: Generally, the effects of morphine may be antagonized by acidifying agents and potentiated by alkalizing agents. The analgesic effect of morphine is potentiated by amphetamines, chlorpromazine and methocarbamol. CNS depressants, such as other opioids, anaesthetics, sedatives, hypnotics, barbiturates, phenothiazines, other tranquilizers, chloral hydrate and glutethimide may enhance the depressant effect of morphine and may result with respiratory depression, hypotension, profound sedation or coma. Monoamine oxidase inhibitors (including procarbazine hydrochloride) should not be taken within two weeks of use. Pyrazolidone antihistamines, beta-blockers and alcohol may also enhance the depressant effect of morphine. When combined therapy is contemplated, the dose of one or both agents should be reduced.

Mixed agonist/antagonist opioid analgesics (i.e., pentazocine, nalbuphine, butorphanol, and buprenorphine) should be administered with caution to a patient who has received or is receiving a course of therapy with a pure opioid agonist analgesic such as morphine. In this situation, mixed agonist/antagonist analgesics may reduce the analgesic effect of morphine and/or may precipitate withdrawal symptoms in these patients.

Morphine may increase the anticoagulant activity of coumarin and other anticoagulants.

ADVERSE REACTIONS

The major hazards associated with morphine, as with other opioid analgesics, are respiratory depression and, to a lesser degree, circulatory depression. Respiratory arrest, shock and cardiac arrest have occurred following oral or parenteral use of morphine.

The most frequently observed side effects of opioid analgesics such as morphine are sedation, nausea, vomiting, constipation, lightheadedness, dizziness, and sweating.

Sedation: Some degree of sedation is experienced by most patients upon initiation of therapy. This may be a least partly because patients often recuperate from prolonged fatigue after the relief of persistent pain. Drowsiness usually clears in three to five days and is usually not a reason for concern providing that it is not excessive, or associated with unsteadiness or confusion. If excessive sedation persists, the reason for it must be sought. Some of these are: concomitant sedative medications, hepatic or renal failure, exacerbated respiratory failure, higher

doses than tolerated in an older patients, or the patient is actually more severely ill than realized. If it is necessary to reduce the dose, it can be carefully increased again after three or four days if it is obvious that the pain is not being well controlled. Dizziness and unsteadiness may be caused by postural hypotension particularly in elderly or debilitated patients. It can be alleviated if the patient lies down. Because of the slower clearance in patients over 50 years of age, an appropriate dose in this age group may be as low as half or less the usual dose in the younger age group.

Nausea and Vomiting: Nausea and vomiting occur frequently after single doses of opioids or as an early unwanted effect of regular opioid therapy. When instituting prolonged therapy for chronic pain, the routine prescription of an antiemetic should be considered. Patients taking a single dose of 20 mg or more of oral morphine every four hours usually require an antiemetic during early therapy. Small doses of prochlorperazine or haloperidol are the most frequently prescribed antiemetics. Nausea and vomiting tend to lessen in a week or so but may persist due to opioid-induced gastric stasis. In such patients, metoclopramide is often useful.

Constipation: Practically all patients become constipated while taking opioids on a persistent basis. In some instances, particularly the elderly or bedridden, fecal impaction may result. It is essential to caution the patients in this regard and to institute an appropriate regimen of bowel management at the start of prolonged opioid therapy. Stool softeners, stimulant laxatives and other appropriate measures should be used as required.

Other Adverse Reactions Include:

Cardiovascular:	faintness, palpitations, postural hypotension, supraventricular tachycardia and syncope
Central Nervous System:	agitation, confusion, dizziness, dysphoria, euphoria, hallucinations, headache, insomnia, involuntary muscle contractions, malaise, mood changes, paresthesia, seizure, somnolence, thought abnormalities, vertigo, vision abnormalities, weakness and withdrawal syndrome
Dermatologic:	edema, pruritus, other skin rashes and urticaria
Endocrine:	a syndrome of inappropriate antidiuretic hormone secretion characterized by hyponatremia secondary to decreased free-water excretion may be prominent (monitoring of electrolytes may be necessary)
Gastrointestinal:	abdominal pain, anorexia, biliary tract spasms, constipation, cramps, dry mouth, dyspepsia, elevated hepatic enzymes, gastrointestinal disorders, ileus, nausea, taste alterations and vomiting

General:	allergic reaction, anaphylactic/anaphylactoid reactions, asthenia, chills, drug dependence, facial flushing, hypertonia, miosis, sweating and tolerance
Genitourinary:	amenorrhea, reduced libido or potency, urinary retention or hesitance
Metabolic and Nutritional:	peripheral edema and pulmonary edema
Respiratory:	bronchospasm and cough decreased

Withdrawal (Abstinence) Syndrome: Physical dependence with or without psychological dependence tends to occur with chronic administration. An abstinence syndrome may be precipitated when opioid administration is discontinued or opioid antagonists administered. The following withdrawal symptoms may be observed after opioids are discontinued: body aches, diarrhea, gooseflesh, loss of appetite, nervousness or restlessness, runny nose, sneezing, tremors or shivering, stomach cramps, nausea, trouble with sleeping, unusual increase in sweating and yawning, weakness, tachycardia and unexplained fever. With appropriate medical use of opioids and gradual withdrawal from the drug, these symptoms are usually mild.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Symptoms: Serious morphine overdosage is characterized by respiratory depression (reduced respiratory rate and/or tidal volume; Cheyne-Stokes respiration; cyanosis), extreme somnolence progressing to stupor or coma, flaccidity of skeletal muscle, cold or clammy skin, and sometimes hypotension and bradycardia. Severe overdosage may result in apnea, circulatory collapse, cardiac arrest and death.

Treatment: Primary attention should be given to the establishment of adequate respiratory exchange through the provision of a patent airway and controlled or assisted ventilation. The opioid antagonist naloxone hydrochloride is a specific antidote against respiratory depression due to overdosage or as a result of unusual sensitivity to morphine. An appropriate dose should therefore be administered, preferably by the intravenous route. The usual initial i.v. adult dose of naloxone is 0.4 mg or higher. Concomitant efforts at respiratory resuscitation should be carried out. Since the duration of action of morphine may exceed that of the antagonist, the patient should be under continued surveillance and doses of the antagonist should be repeated as needed to maintain adequate respiration.

An antagonist should not be administered in the absence of clinically significant respiratory or cardiovascular depression. Oxygen, intravenous fluids, vasopressors and other supportive measures should be used as indicated.

In an individual physically dependent on opioids, the administration of the usual dose of opioid antagonist will precipitate an acute withdrawal syndrome. The severity of this syndrome will depend on the degree of physical dependence and the dose of antagonist administered. The use of opioid antagonists in such individuals should be avoided if possible. If an opioid antagonist must be used to treat serious respiratory depression in the physically dependent patient, the antagonist should be administered with extreme care by using dosage titration, commencing with 10 to 20% of the usual recommended initial dose.

Evacuation of gastric contents may be useful in removing unabsorbed drug.

DOSAGE AND ADMINISTRATION

Administration and dosing of morphine should be individualized bearing in mind the properties of the drug. In addition, the nature and severity of the pain or pains experienced, and the total condition of the patient must be taken into account. Of special importance is other medication given previously or concurrently.

As with other strong opioid analgesics, use of morphine for the management of persistent pain should be preceded by a thorough assessment of the patient and diagnosis of the specific pain or pains and their causes. Use of opioids for the relief of chronic pain, including cancer pain, all important as it may be, should be only one part of a comprehensive approach to pain control including other treatment modalities or drug therapy, non-drug measures and psychosocial support.

Adult Dose: Individual dosing requirements vary considerably based on each patient's age, weight, severity of pain, and medical and analgesic history.

The most frequent initial dose is 10 mg every 4 hours as needed for acute pain and every 4 hours around the clock for chronic pain, or as directed by a physician. The suppository may be used in situations where the patient cannot tolerate oral dosing, at the same dosage and frequency.

Patients over the age of 50 tend to require much lower doses of morphine than in the younger age group. In elderly and debilitated patients and those with impaired respiratory function or significantly decreased renal function, the initial dose should be one half the usual recommended dose.

Patients Currently Receiving Opioids: For patients who are receiving an alternate opioid, the "oral morphine sulfate equivalent" of the analgesic presently being used should be determined. Having determined the total daily dosage of the present analgesic, the following equivalence table can be used to calculate the approximate daily oral morphine sulfate dosage that should provide equivalent analgesia.

Dose Titration: Dose titration is the key to success with morphine therapy. **Proper optimization of doses scaled to the relief of the individual's pain should aim at the regular administration of the lowest dose of morphine which will maintain the patient free of pain at all times.**

Dose adjustments should be based on the patient's clinical response. Higher doses may be justified in some patients to cover periods of physical activity.

Adjustment or Reduction of Dosage: Following successful relief of severe pain, periodic attempts to reduce the opioid dose should be made. Smaller doses or complete discontinuation may become feasible due to a change in the patient's condition or improved mental state. If treatment discontinuation is required, the dose of opioid may be decreased as follows: one-half of the previous daily dose given q4h for the first two days, followed thereafter by a 25% reduction every two days.

Opioid analgesics may only be partially effective in relieving dysesthetic pain, post-herpetic neuralgia, stabbing pains, activity-related pain, and some forms of headache. This is not to say that patients with advanced cancer suffering from some of these forms of pain should not be given an adequate trial of opiate analgesics, but it may be necessary to refer such patients at an early time for other forms of pain therapy.

TABLE 1
OPIOID ANALGESICS: APPROXIMATE ANALGESIC EQUIVALENCES[1]

Drug	Equivalent Dose (mg)[2] (compared to morphine 10 mg IM)		Duration of Action (hours)
	Parenteral	Oral	
Strong Opioid Agonists:			
Morphine	10	60[3]	3-4
Oxycodone[4]	15	30	2-4
Hydromorphone	1.5	7.5	2-4
Anileridine	25	75	2-3
Levorphanol	2	4	4-8
Meperidine[6]	75	300	1-3
Oxymorphone	1.5	5 (rectal)	3-4
Methadone[5]	-	-	-
Heroin	5-8	10-15	3-4
Weak Opioid Agonists:			
Codeine	120	200	3-4
Propoxyphene	50	100	2-4
Mixed Agonist-Antagonists[7]:			
Pentazocine[6]	60	180	3-4
Nalbuphine	10	-	3-6
Butorphanol	2	-	3-4

[1]References:

Expert Advisory Committee on the Management of Severe Chronic Pain in Cancer Patients, Health and Welfare Canada. Cancer pain: A monograph on the management of cancer pain. Ministry of Supplies and Services Canada, 1987. Cat. No. H42-2/5-1984E.
Foley KM. The treatment of cancer pain. N Engl J Med 1985;313(2):84-95.
Aronoff GM, Evans WO. Pharmacological management of chronic pain: A review. In: Aronoff GM, editor. Evaluation and treatment of chronic pain. 2nd ed. Baltimore (MD): Williams and Wilkins; 1992. p. 359-68.
Cherny NI, Portenoy RK. Practical issues in the management of cancer pain. In: Wall PD, Melzack R, editors. Textbook of pain. 3rd ed. New York: Churchill Livingstone; 1994. p. 1437-67.

[2] **Most of the data were derived from single-dose, acute pain studies and should be considered an approximation for selection of doses when treating chronic pain.**

[3] **For acute pain, the oral or rectal dose of morphine is six times the injectable dose. However, for chronic dosing, clinical experience indicates that this ratio is 2 - 3: 1 (i.e., 20-30 mg of oral or rectal morphine is equivalent to 10 mg of parenteral morphine).**

[4] Based on single entity oral oxycodone in acute pain.

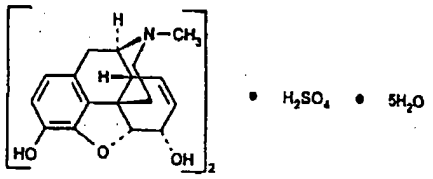
[5] Extremely variable equianalgesic dose. Patients should undergo individualized titration starting at an equivalent to 1/10 of the morphine dose.

[6] Not recommended for the management of chronic pain.

[7] Mixed agonist-antagonists

PHARMACEUTICAL INFORMATION

The chemical name of morphine sulfate is 7,8,-didehydro-4,5 α-epoxy-17-methyl-morphinan-3, 6α-diol sulfate (2:1) (salt) pentahydrate, and it has the following structure:



Molecular Formula: $(C_{17}H_{19}NO_3) - H_2SO_4$

Molecular Weight: 758.8 (pentahydrate)
668.8 (anhydrous)

Description: Morphine sulfate is a white, odourless crystalline powder or needlelike crystals. Morphine sulfate is soluble 1:21 in water and 1:1000 in ethanol. It is practically insoluble in ether or chloroform.

Composition:

Active ingredient(s): Morphine Sulfate

Non-medicinal Ingredients *(all strengths)*: croscarmellose sodium, hydroxypropyl methylcellulose, lactose, magnesium stearate, microcrystalline cellulose and polyethylene glycol 400

AVAILABILITY

MS•IR® (morphine sulfate pentahydrate) is available as white, film-coated immediate-release tablets in four strengths:

5 mg: Scored round tablets with "5" engraved on one side and "PF" on the other.

10 mg: Scored round tablets with "10" engraved on one side and "PF" on the other.

20 mg: Scored caplet-shaped tablets with "20" engraved on one side and "PF" on the other.

30 mg: Scored caplet-shaped tablets with "30" engraved on one side and "PF" on the other.

Supplied in opaque plastic bottles of 50 tablets.

Stability and Storage Recommendations:

Store tablets at room temperature (15 - 30° C).

INFORMATION FOR THE CONSUMER

Read this information carefully before you take MS•IR® tablets. Also read the information you get with your prescription refills, since there may be something new. This information does not take the place of talking with your doctor about your medical condition or your treatment. Only you and your doctor can decide if MS•IR is right for you. Share the information in this leaflet with members of your household.

What is morphine?

Morphine is a medicine used to treat severe pain and should help you live more comfortably and independently. Morphine belongs to a class of drugs which is commonly referred to as opiates, opioids or narcotics, and also includes codeine, fentanyl, hydromorphone and oxycodone.

Your pain may increase or decrease from time to time and your doctor may need to change the amount of morphine you take daily (daily dosage).

What is MS•IR?

MS•IR is an immediate release tablet containing the medicine morphine, to treat severe pain. MS•IR is made to release morphine promptly, usually requiring dosing every 4 hours to control pain.

MS•IR tablets are available as white film-coated immediate-release tablet in four strengths: 5 mg, 10 mg, 20 mg, and 30 mg. It may be necessary for you to take more than one tablet strength at the same time, in order to receive the total daily dosage prescribed by your doctor.

Before you take MS•IR:

Your doctor should know about all of your medical conditions before deciding if MS•IR is right for you and what daily dosage is best. Tell your doctor about all of your medical problems, especially the following ones: trouble breathing or lung problems; head injury; liver or kidney problems; gastrointestinal problems; low blood pressure; prostate problems; urethral stricture (unusual narrowing of the urethra); adrenal gland problems, such as Addison's disease; convulsions or seizures; alcoholism; hallucinations or other severe mental problems; past or present substance abuse or drug addiction.

You should also tell your doctor if you are pregnant, breast-feeding, or intend to become pregnant while receiving MS•IR as this drug may not be right for you in these circumstances.

MS•IR should not be used if:

- your doctor did not prescribe it for you;
- your pain is mild;
- you have experienced severe allergic reactions (e.g., severe rash, hives, breathing problems, swelling of the mouth, tongue, face, or other areas or dizziness) while taking any opioid, including morphine, or any of the non-medicinal ingredients, in the past;

- you have severe asthma or severe lung problems;
- you have an irregular heartbeat;
- you suffer from alcoholism;
- you have a head injury;
- you have a brain tumour;
- you suffer from seizures.

How to take MS•IR:

You should not consume alcohol while taking MS•IR, as it may increase the chance of experiencing dangerous side effects.

Follow your doctor's directions exactly. **MS•IR** tablets must be taken regularly, usually every 4 to 6 hours (with 4 to 6 oz. of water), as directed by your doctor. If your pain worsens, making you uncomfortable, contact your doctor immediately and she/he may decide that it is necessary to adjust your daily dosage of **MS•IR** tablets.

Your daily dosage of **MS•IR** will be clearly labelled on the medication bottle. Be sure to follow these directions exactly; this is very important. Do not increase or decrease your daily dosage without consulting your doctor. If your daily dosage is changed by your doctor, be sure to write it down at the time your doctor calls you or sees you and follow the new directions exactly. Regularly discuss your pain control and any side effects with your doctor, to determine if you still need **MS•IR**. Be sure to use **MS•IR** only for the condition for which it was prescribed.

Stopping MS•IR:

Consult your doctor for instructions on how to discontinue taking **MS•IR**. You should not stop taking **MS•IR** all at once if you have been taking it for more than a few days, since this may lead to uncomfortable symptoms.

After you stop taking **MS•IR**, you should take the unused tablets to your pharmacist to be destroyed.

Side effects you may have while taking MS•IR:

The most common side effects you may experience are constipation, nausea, drowsiness, dizziness, vomiting, itching, headache, dry mouth, weakness and sweating. Tell your doctor about these problems if they arise. Your doctor may prescribe a laxative and/or stool softener to help relieve constipation while you are taking **MS•IR**.

If you experience any symptoms related to difficulty in breathing, such as tight chest or wheezing, fainting, or rapid heartbeat, tell your doctor or pharmacist immediately.

Overdose:

The most important signs of overdose are suppressed breathing (abnormally slow or weak breathing), dizziness, confusion, or extreme drowsiness. In case of suspected overdose, or if any of these symptoms occur, call your doctor and/or your local emergency number immediately.

Taking MS•IR with other medications:

You should not take MS•IR if you are currently taking (or recently stopped taking) one of the medicines known as monoamine oxidase inhibitors (e.g. Nardil®, Parnate®).

Tell your doctor about all medicines that you are taking. Your doctor should decide whether you can take MS•IR with other medicines. These include:

- other opioids, anaesthetics, sedatives, hypnotics, barbiturates, phenothiazines, amphetamines, chlorpromazine, methocarbamol, tranquilizers, some heart medications (e.g., beta-blockers), blood-thinners (coumarin or other anticoagulants), chloral hydrate and glutethimide (not available in Canada);
- antihistamines or sleep aids (these medicines could depress your breathing or your level of consciousness);
- medicines that you buy yourself without a prescription;
- any herbal remedies that you may be taking.

Driving/Other Activities:

Driving, operating hazardous machinery, or other tasks requiring full alertness should not be attempted for the first few days of taking MS•IR, or after your daily dosage is changed, since you may experience drowsiness or sedation. If drowsiness or sedation occurs, do not undertake such activities until you have talked with your doctor.

Abuse, Addiction and Physical Dependence:

There is a risk of abuse or addiction with all opioids. Some patients, particularly those who may have abused drugs in the past, may have a higher risk of abusing or developing an addiction while taking opioids, such as MS•IR.

Patients who have taken MS•IR for a period of time may develop physical dependence, and should not abruptly stop taking it. However, physical dependence is not the same as addiction.

If you have concerns about abuse, addiction or physical dependence, please tell your doctor.

Reordering MS•IR:

A new written prescription is required from your doctor each time you need more MS•IR. Therefore, it is important that you contact your doctor at least three working days before your current supply runs out.

It is very important that you do not miss any doses. If you miss one dose, take it as soon as possible, but if it is almost time for your next dose, then skip the missed dose. Do not take two doses at once, unless your doctor tells you to. If you miss several doses in succession, talk to your doctor before restarting.

Do not seek additional prescriptions for MS•IR from any other doctor - unless responsibility for your pain management has been transferred to another doctor.

Should your pain increase, or any other complaint develop as a result of taking MS•IR, tell your doctor immediately.

Storage of MS•IR:

MS•IR contains an opioid medicine and must be stored in a secure place to prevent theft and misuse. Do not give MS•IR to anyone other than the person for whom it was prescribed since it may seriously harm them. Keep MS•IR out of the reach of children. Accidental overdose by a child is dangerous and may result in death. Keep MS•IR in a cool, dry place, between 15 and 30°C.

This leaflet summarizes important information about MS•IR. If you would like more information, talk with your doctor and/or pharmacist or contact the manufacturer, Purdue Pharma, at 1-800-387-5349.

Reference 2.4

GOODMAN & GILMAN'S The PHARMACOLOGICAL BASIS OF THERAPEUTICS

Ninth Edition

McGraw-Hill
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Table 23–2
Actions and Selectivities of Opioids at the Various Opioid Receptor Classes

	RECEPTOR TYPES			
	μ	δ	κ_1	κ_3
Drugs				
Morphine	+++		+	+
Methadone	+++			
Etorphine	+++	+++	+++	+++
Levorphanol	+++		NA	+++
Fentanyl	+++			
Sufentanil	+++	+	+	
DAMGO	+++			+
Butorphanol	P	NA	+++	NA
Buprenorphine	P	NA	−−	NA
Naloxone	−−−	−	−−	−−
Naltrexone	−−−	−	−−−	−−
CTOP	−−−			−
Diprenorphine	−−−	−−	−−−	−−−
β-Funaltrexamine	−−−	−	++	NA
Naloxonazine	−−−	−	−	−
Nalorphine	−−−		+	+++
Pentazocine	P		++	+
Nalbuphine	−−		++	++
Naloxone benzoylhydrazone	−−−	−	−	+++
Bremazocine	+++	++	+++	++
Ethylketocyclazocine	P	+	+++	+++
U50,488			+++	
U69,593			+++	
Spiradoline	+		+++	
nor-Binaltorphimine	−	−	−−−	−
Naltrindole	−	−−−	−	−
DPDPE		++		
[D-Ala^2,Glu^4]deltorphin		++		
DSLET	+	++		
Endogenous Peptides				
Met-enkephalin	++	+++		
Leu-enkephalin	++	+++		
β-Endorphin	+++	+++		
Dynorphin A	++		+++	NA
Dynorphin B	+	+	+++	NA
α-Neoendorphin	+	+	+++	NA

Activities of drugs are given at the receptors for which the agent has reasonable affinity. +, agonist; −, antagonist; P, partial agonist; NA, data not available or inadequate; DAMGO, CTOP, DPDPE, DSLET, *see* Table 23–1. The number of symbols is an indication of potency; the ratio for a given drug denotes selectivity. These values were obtained primarily from animal studies and should be extrapolated to human beings with caution. Both β-funaltrexamine and naloxonazine are irreversible μ antagonists, but β-funaltrexamine also has reversible κ agonist activity.

Table 23–3
Classification of Opioid Receptor Subtypes and Actions from Animal Models

	RECEPTOR SUBTYPE	AGONISTS	ANTAGONISTS
Analgesia			
Supraspinal	μ_1, κ_3, δ_1, δ_2,	Analgesic	No effect
Spinal	μ_2, δ_2, κ_1	Analgesic	No effect
Respiratory function	μ_2	Decrease	No effect
Gastrointestinal tract	μ_2, κ	Decrease transit	No effect
Psychotomimesis	κ	Increase	No effect
Feeding	μ, κ, δ	Increase feeding	Decrease feeding
Sedation	μ, κ	Increase	No effect
Diuresis	κ_1	Increase	
Hormone regulation			
Prolactin	μ_1	Increase release	Decrease release
Growth hormone	μ_2 and/or δ	Increase release	Decrease release
Neurotransmitter release			
Acetylcholine	μ_1	Inhibit	
Dopamine	μ_2, δ	Inhibit	
Isolated organ bioassays			
Guinea pig ileum	μ_2	Decrease	No effect
Mouse vas deferens	δ	Decrease	No effect

The actions listed for antagonists are seen with the antagonist alone. The subtypes responsible for a number of actions attributed to a general family of receptor have not been identified. All the correlations in this table are based on studies in rats and mice, which occasionally show species differences. Thus, any extensions of these associations to human beings are tentative. Clinical studies do indicate that μ receptors elicit analgesia both spinally and supraspinally, but the subtypes have not been identified. Preliminary work with a synthetic opioid peptide, [D-Ala^2,D-Leu^5]enkephalin, suggests that intrathecal δ agonists are analgesic in human beings.

SOURCE: Modified from Pasternak (1993).

κ_1 receptor. Administration of U50,488H spinally elicits analgesia in animal models. κ_2 Receptors were proposed from binding studies, but their pharmacological properties remain unknown. κ_3 Receptors also were first identified in binding studies (Clark *et al.*, 1989), and their pharmacological properties are moderately well established (*see* Pasternak, 1993). Unlike κ_1 receptors, which produce analgesia spinally, κ_3 receptors relieve pain through supraspinal mechanisms. Although effects of κ_3 receptors are readily reversed by a number of opioid antagonists, no κ_3-selective antagonists have been identified. κ_3 Receptors correspond to Martin's nalorphine (N) receptors (Martin and Sloan, 1977; Paul *et al.*, 1991).

Delta Receptors. The enkephalins are the endogenous ligands for δ receptors. Our understanding of δ receptor pharmacology has relied heavily on the development of highly selective agonists and antagonists, such as naltrindole. Using these drugs, investigators have established δ analgesia both spinally and supraspinally, although the spinal system appears to be more robust. Two subclasses, δ_1- and δ_2-opioid receptors, have been proposed based on their differential sensitivity to blockade by several novel antagonists (Portoghese *et al.*, 1992; Sofuoglu *et al.*, 1991). The agonists [D-Pro^2,Glu^4]deltorphin and DSLET preferentially bind to δ_2 receptors, whereas DPDPE has higher affinity for δ_1 receptors.

Molecular Cloning of Opioid Receptors. Members of each class of opioid receptor have been cloned from human cDNA and their predicted amino acid sequences obtained (*see* Figure 23–2 and Table 23–4). Their amino acid sequences are approximately 65% identical, and they have little sequence similarity to other G protein–coupled receptors, except receptors for somatostatin (Reisine and Bell, 1993). The regions of highest similarity in sequence are the sequences predicted to lie in the seven transmembrane-spanning regions and the intracellular loops. Regions of amino acid sequence divergence are the amino and carboxy termini and the second and third extracellular loops. The extracellular regions that differ in amino acid sequence may contain the unique ligand-binding domains of each receptor, whereas the different intracellular domains may be involved in their differential regulation and may contribute to variations in their coupling to effector systems. As the human opioid receptor genes have multiple introns, subtypes of μ, κ, and δ receptors may result from alternative splicing.

The functional significance of the cloned receptors has been established with antisense approaches in rodent model systems. Using

Reference 3

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POTENT ANTINOCICEPTIVE EFFECTS OF TRK-820, A NOVEL κ-OPIOID RECEPTOR AGONIST

Takashi Endoh[1], Hirotoshi Matsuura[1], Atsushi Tajima[1], Naoki Izumimoto[1], Chiko Tajima[1], Tomohiko Suzuki[1], Akiyoshi Saitoh[1], Tsutomu Suzuki[2], Minoru Narita [3], Leon Tseng [3] and Hiroshi Nagase [1]

[1]Basic Research Laboratories, Toray Industries, Inc. 1111, Tebiro Kamakura, Kanagawa 248-8555, Japan, [2]Department of Pharmacology, School of Pharmacy, Hoshi University, Sinagawa-ku Tokyo, 142 Japan, [3]Department of Anesthesiology, Medical College of Wisconsin, Milwaukee, WI 53226, USA.

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Summary

TRK-820, a new type of 4,5-epoxymorphinan derivative, was investigated *in vivo* for antinociceptive activities and its selectivity on various opioid receptors in mice. TRK-820 given s.c. or p.o. was found to be 351- and 796-fold more potent than U50,488H with acetic acid-induced abdominal constriction test. The duration of the antinociceptive effect produced by TRK-820 was longer than that produced by μ-opioid receptor agonist morphine or other κ-opioid receptor agonists. In addition, with four other antinociceptive assays, low temperature hot plate (51 °C), thermal tail flick, mechanical tail pressure and tail pinch tests, TRK-820 was also found to be 68- to 328-fold more potent than U-50488H, and 41- to 349-fold more potent than morphine in producing antinociception, as comparing the weight of the different compound. However, TRK-820 was less active in inhibiting the high temperature (55° C) hot plate response. The antinociceptive effects produced by TRK-820 were inhibited by nor-BNI, but not by naloxone or naltrindole (NTI) with the abdominal constriction test, indicating that the antinociception is selectively mediated by the stimulation of κ-, but not μ- or δ- opioid receptors. Co-administration of TRK-820 with morphine slightly enhanced the antinociception induced by morphine in the mouse hot plate test. On the other hand, pentazocine significantly reduced the morphine-induced antinociception. TRK-820 produced sedation at doses, which are much higher than the doses for producing antinociception. These results indicate that the potent antinociception induced by TRK-820 is mediated via the stimulation of κ-, but not μ- or δ-opiod receptors.

Key Words: κ agonist, antinociception, opioid receptor, TRK-820

Opioid receptors have been classified into μ-, δ- and κ-opioid receptors based on their different pharmacological profiles in chronic spinal dogs (1), isolated tissues and radioligand bindings in brain membrane preparation (2,3,4). Although μ opioid receptor agonists such as morphine and fentanyl are clinically important in the treatment of pain, they are associated with undesirable side effects, including respiratory depression (5), constipation (6,7) and dependence liability (8). On the other hand, κ-opioid receptor agonists such as U-50488H (9), U-69593 (10),

[1]Correspondence to:[e-mail]Takashi_Endo@nts.toray.co.jp

PD-117302 (11), and CI-977 (12) produce antinociceptive effects in animal models without the morphine-like side effects. However, they cause dysphoria and psychotomimetic effects. These κ-agonists have common chemical structures such as the [N-C-C-N(SP2)] pharmacophore sequence. They do not have tyrosine-glycine moiety, which is essential for opioid activity of the endogenous opioid peptides. We, therefore, designed a new type of κ-opioid receptor agonist with a novel chemical structure, which contains a tyrosine-glycine moiety in an attempt to eliminate the side effects shared by arylacetamide series. We have successfully synthesized a compound, TRK-820 (13) which is a (-)-17-cyclopropylmethyl-3,14b-dihydroxy-4,5a-epoxy-6b-[N-methyl-trans-3-(3-furyl)acrylamide] morphinan hydrochloride. This morphinan analogue is a potent and selective κ-opioid receptor agonist in *in vitro* experiments with guinea pig ileum and mouse vas deferens preparations (13). The present study demonstrates that TRK-820 is a selective κ-opioid receptor agonist, which produces antinociceptive effects selectively by the stimulation of κ-, but not μ- or δ-opioid receptors.

Materials and methods

Animals

Male ddY mice (Japan SLC), 4-5 weeks of age, were used. Animals were housed 5 per cage with food and water freely available in an room maintained at 22° C with an alternating 12-h light/dark cycle. Ten to 20 mice were used per treatment group.

Antinociceptive tests

Abdominal constriction test: Abdominal constriction was induced by the injection of 0.6 % of acetic acid (10 ml/kg body weight, i.p.). An abdominal constriction was defined as a wave of contraction of the abdominal musculature followed by extension of the hind limbs. Acetic acid solution was injected i.p. 30 min after the administration of the opioid drug being studied and the number of abdominal constriction was counted for 10 min after acetic acid administration. Percent analgesia was expressed as: 100 x (No. of mean control abdominal constriction - No. of test abdominal constriction) / No. of mean control abdominal constriction.

To determine time course of antinociceptive activity mice were dosed with each drug subcutaneously and nociceptive response determined at one of the following time intervals: 15, 30, 60, 180 and 240 min. Each mouse was used for only once during this study.

Hot plate tests: To hot plate (MK-350; Muromachi, Japan) tests were used at high temperature (55.0°C ; ranging from 54.8°C to 55.2°C) and low temperature (51.0°C ; ranging from 50.8°C to 51.2°C). Mice were placed on the heated smooth surface, and the latency to licking, shaking of the limbs or jumping was measured. Prior to drug administration, the nociceptive response of each mouse was measured three times. The first measurement was omitted and the mean of the 2nd and 3rd responses was used as pre-drug latency for each mouse. The cut-off times of 30 sec for the high temperature 55 °C hot plate test and 60 sec for the low temperature 51.0°C hot plate test were used in these tests to minimize tissue damage.

Tail flick test: Mice responded to a focused heat stimulus by flicking or removing their tail from the path of the stimulus, thereby exposing a photocell located in the tail flick analgesia meter (MK-330A; Muromachi) immediately below the tail. The reaction time was automatically recorded. Prior to dosing, the nociceptive threshold was measured three times, and the mean of the last two measurement of reaction times was used as pre-drug latency for each mouse. The cut-off time of 10 sec was used to prevent tissue damage.

Tail pressure test: Mechanical nociceptive thresholds were measured by the Randall-Selitto pressure test (14) using an analgesimeter (Ugo basile, Italy). In this test, pressure is applied about 1.5 cm caudal from the base of tail of mice at a linearly increasing rate of 32 g/sec, and the pressure (g) required to elicit the tail-withdrawal response of each mouse was determined and

defined as the nociceptive threshold. A cut-off threshold of 500 g (based on control thresholds of 80 to 200 g) was used to prevent tail damage. Prior to drug injection, the nociceptive threshold was measured three times at intervals of 30-60 min. The first measurement was omitted and the mean of the next two was used as pre-drug threshold for each mouse.

Tail pinch test: A bulldog clamp was applied as a nociceptive stimulus to the base of the tail of the mice. Loss of the turning response to the stimulus was taken as the criterion for antinociception and the latency to this turning response was recorded. Prior to administration of the compounds, the nociceptive threshold for each mouse was measured twice at a 30-min interval and the mean was used as pre-drug latency value. The basal latency was approximately 2 sec for each mouse. The bulldog clamp was released 15 sec after the beginning of this test, without excessive tissue injury. Each mouse was used only once during this study.

Experimental protocols

Antinociception was determined by the mouse acetic acid-induced abdominal constriction test. The antinociceptive test with or without opioid receptor antagonists was performed 30 min after the s.c. administration of TRK-820, morphine or U-50488H and 15 min after the i.c.v. administration of DPDPE. Naloxone and naltrindole (NTI) was co-administered subcutaneously with TRK-820, morphine or U-50488H. When DPDPE was used, NTI was administered 15 min before the DPDPE injection. Nor-binaltorphimine (Nor-BIN) was administered subcutaneously approximately 24 hr before the injection of each agonist.

TRK-820 was co-administered with morphine to clarify the influence of TRK-820 on morphine analgesia in the mouse hot plate test, and compared with an interaction with morphine and pentazocine, agonist/antagonist.

Rotarod test in mice

Mice were trained to maintain their position on a rotarod 3 cm in diameter, at 8 rpm for 60 sec or more using the Rotarod apparatus (KN-75; Natsume). The basal time required for each mouse to fall off the rotarod was measured twice and the mean was used as pre-drug value. Mice which have pre-drug values of less than 60 sec should not be used for this test because of avoiding the increase in a variation from mouse to mouse in the time placed on the rotarod. The time duration for each mouse to fall off the rotarod was recorded. The cut-off was set at 300 sec. If a mouse that had been injected with the test agents or vehicle fell within 60 sec, the time required to fall off the rotarod was measured again and the mean of two trials was the test response time for each mouse.

Data analysis

The individual latency or threshold was converted to percent analgesia according to the following formula: % analgesia = (T1 - T0)/(T2 - T0) x 100, where T0 is pre-drug latency or threshold, T1 is the latency or threshold after dosing, and T2 is the cut-off. All data represent the mean percent analgesia ± S.E.M. The dose that produced 50 % analgesia was taken as the antinociceptive ED_{50} values for each agonist, calculated from the log-dose vs. percent analgesia data by linear regression techniques (15). Four to 5 doses per each drug and 10-20 mice per each dose were used for the ED_{50} determination. Differences between morphine alone and morphine + pentazocine or TRK-820 were determined by Dunnett's multiple range test (JMP version 3.1, SAS Institute).

Materials

The following drugs were used in this study. TRK-820 (Lot No. TN-101), ICI-199441 (16), PD-117302 (17), nor-BNI (18) and NTI (19), (synthesized in Toray Industries, Inc., Japan) were

dissolved in distilled water (Otsuka, Japan). CI-977 (12) (synthesized at Toray Industries, Inc.) and U-69593 (Sigma, USA) were dissolved in 10% dimethyl sulfoxide (Kokusan Chemical,Japan) / distilled water (Otsuka, Japan). U-50488H (20) (synthesized in Toray Research Center, Inc.), naloxone(RBI), morphine (Takeda Chemical Industries), pentazocine (Sankyo, Japan) and DPDPE (Sigma) was dissolved in distilled water (Otsuka).

All doses are observed as the salt form of the drug.

Results

Antinociceptive effects of TRK-820 and other opioid agonists given s.c. or p.o.

TRK-820 (5–40 μg/kg) given s.c. caused a dose-dependent increase of the inhibition of the acetic acid-induced abdominal constriction. The inhibition of the abdominal constriction reached its peak 30 min after injection, gradually declined and returned to the preinjection level 4 hr after the injection. U-50488H, CI-977, ICI-199441 or morphine given s.c. also inhibited the abdominal constriction. However, the inhibition reached its peak 30 min, rapidly declined and returned to the preinjection level in 120 - 180 min (Fig 1). Similar time courses on the production of antinociception by these opioids when given p.o. were also observed. The antinociceptive ED_{50} values for TRK-820 were estimated to be 3.3 and 32 μg/kg given s.c. and p.o., which were 351- and 796-fold more potent than U-50488H and 175- and 187-fold more potent than morphine given s.c. and p.o., respectively. Compared with the other κ compounds, TRK-820 appears to be more readily absorbed orally based on the p.o. ED_{50}/ s.c. ED_{50} ratio of 9.7. This value is much lower than values for the other κ-opioid receptor agonists, U-50488H, CI-977, ICI-199441 and PD-117302, which are ranged from 22 to > 145. The κ-opioid receptor agonists CI-977 and ICI-199441 given s.c. displayed similar antinociceptive potency to TRK-820. However, these two compounds were much less potent than TRK-820 after p.o. administration (Table 1).

Table 1
Antinociceptive effects in the mouse acetic acid-induced abdominal constriction test.

Compounds	Antinociceptive ED_{50} s.c. mg/kg	p.o.	p.o.ED_{50} /s.c.ED_{50}	Duration (s.c.) hrs
TRK-820	0.0033 (0.0025-0.0043)	0.032 (0.025-0.041)	9.7	3-4
U-50488H	1.16 (0.90-1.51)	25.5 (20.6-31.5)	22.0	1
CI-977	0.0069 (0.0052-0.0092)	>1.0	>145	1
ICI-199441	0.0071 (0.0052-0.0096)	0.30 (0.25-0.37)	42.3	2
PD-117302	1.22 (0.94-1.57)	33.0 (27.8-39.1)	27.0	n.t.
Morphine	0.58 (0.48-0.71)	6.01 (4.91-7.37)	10.4	2

The antinociceptive ED50 value of each drug was calculated from data 30 min after s.c. or p.o. dosing. Parentheses: 95% confidence limits. n.t.: not tested

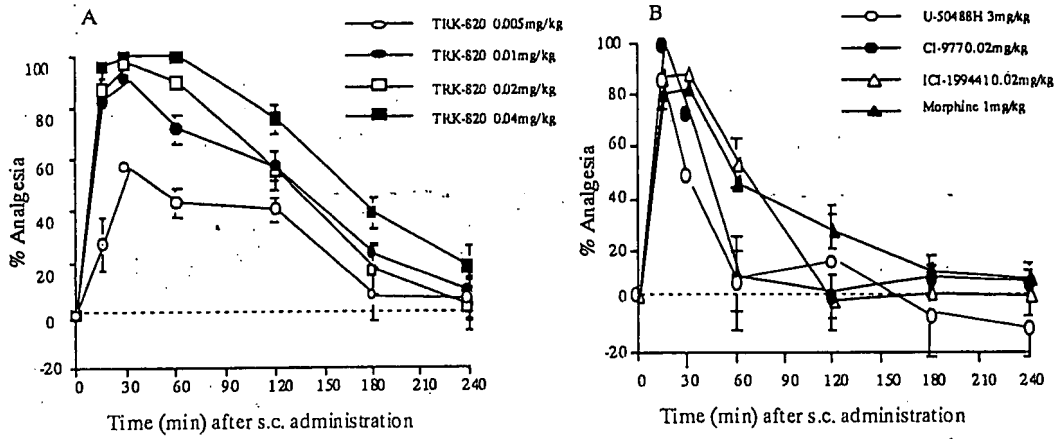

Fig. 1

Time courses of the inhibition of the acetic acid-induced abdominal constriction after s.c. injection of TRK-820 (A) and other κ -agonists (U-50488H, CI-977,ICI-199441) and morphine (B) Each value represents the mean ± S.E.M. from 10-20 mice.

TRK-820 given s.c. also produced a dose-dependent antinociception with the low temperature hot plate, tail flick, tail pressure, and tail pinch tests. With the exception of the hot plate tests, the potencies for TRK-820 with these antinociceptive tests are comparable to that with acetic acid-induced abdominal constriction test. TRK-820 was found to be less active in inhibiting the low temperature (51° C) hot plate response, and not active in inhibiting a high temperature (55° C) hot plate response. The ED_{50} for TRK-820 for inhibiting the low temperature hot plate response was found to be 39-fold greater than the value with the acetic acid-induced abdominal constriction test (129 μg/kg with low temperature hot-plate test vs. 3.3 μg/kg with acetic acid-induced abdominal constriction test) and TRK-820 even at a high dose 0.2 mg/kg only produced 32 % analgesia.

Table 2

Antinociceptive effects in the high (55 °C), low temperature (51°C) hot plate, tail flick, tail pressure and tail pinch tests in mice.

Compounds	High temperature hot plate	Low temperature hot plate	Tail flick	Tail pressure	Tail pinch
		Antinociceptive ED_{50} (mg/kg, s.c.)			
TRK-820	32.0% at 0.2	0.129 (0.100-0.166)	0.062 (0.032-0.119)	0.0090 (0.051-0.016)	0.035 (0.017-0.073)
U-50488H	63.8% at 20	8.71 (5.88-12.9)	5.18 (2.35-11.42)	1.0 (0.69-1.4)	11.5 (6.9-19.0)
ICI-199441	n.t.	0.065 (0.042-0.100)	0.042 (0.025-0.070)	0.024 (0.018-0.031)	0.051 (0.029-0.091)
U-69593	n.t.	1.33 (0.73-2.46)	n.t.	0.48 (0.35-0.67)	2.8 (1.8-4.3)
Pentazocine	44.6% at 40	52.2 (35.8-76.0)	n.t.	n.t.	n.t.
Morphine	3.65 (3.04-4.39)	5.30 (4.12-6.81)	5.26 (3.79-7.32)	1.5 (1.1-2.0)	12.2 (2.5-58.2)

The antinociceptive ED_{50} value of each drug was calculated from data 30 min after s.c. dosing.
Parentheses:95% confidence limits, n.t.: not tested

The effects of treatment with selective opioid receptor antagonsits on the antinociception induced by TRK-820.

The experiments were designed to identify the types of the opioid receptors, which are involved in antinociception induced by TRK-820 using acetic acid-induced abdominal constriction assay. Subcutaneous administration of TRK-820 at doses 1-10 μg/kg caused a dose-dependent inhibition of the abdominal constriction response. Subcutaneous pretreatement with nor-BNI 20 mg/kg antagonized the antinociception induced by TRK-820 and the dose-response curve of TRK-820 were shifted to the right by 39-fold. Pretreatment with naloxone or NTI did not affect the antinociception induced by s.c. administration of TRK-820. Similar results were obtained with U-50488H. The antinociception induced by U-50488H was significantly blocked by the s.c. pretreatment with nor-BNI, but not by naloxone 0.3 mg/kg or NTI 3 mg/kg. Subcutaneous administration of morphine at doses 0.25-2 mg/kg caused a dose-dependent inhibition of the abdominal constriction. The antinociception induced by morphine was not affected by subcutaneous pretreatement with nor-BNI or NTI, but was significantly antagonized by the s.c. pretreatment with naloxone. The same dose of NTI 3 mg/kg, which did not affect the antinocicetion of TRK-820, U50,488H, or morphine, was found to significantly attenuate the antinociception induced by DPDPE given intracerebroventricularly, and the dose-response curve of DPDPE was shifted to the right by 6-fold (Table 3, Fig. 2).

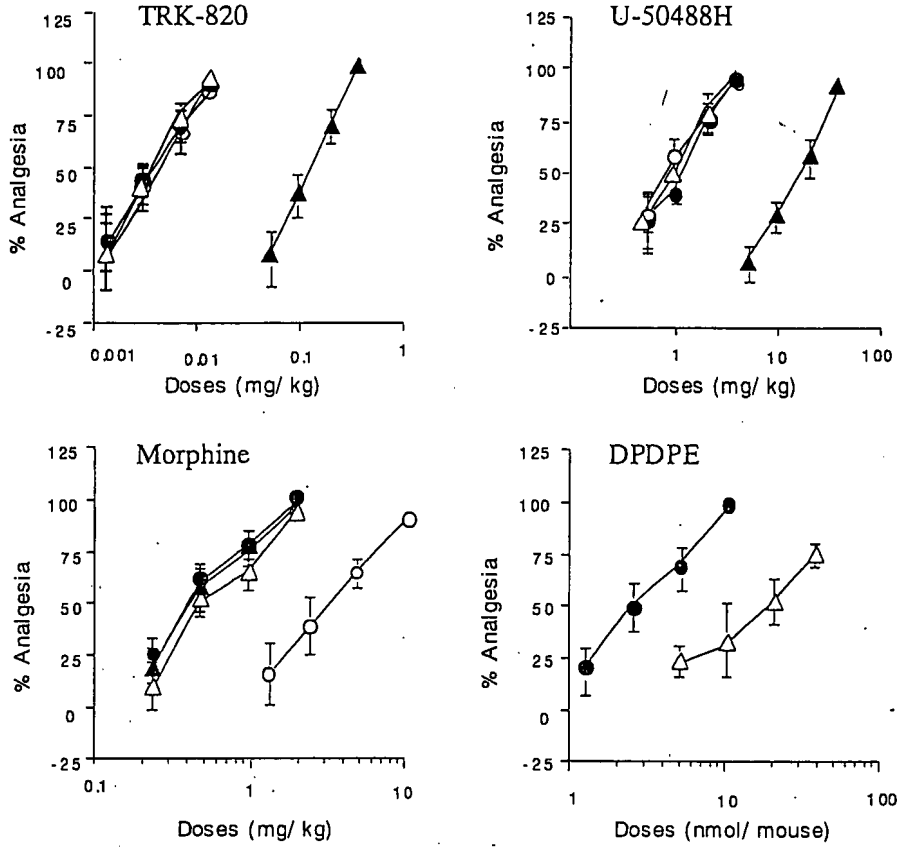

Fig. 2

Effects of nor-BNI, naloxone and NTI on the antinociceptive action by TRK-820, U-50488H, morphine and DPDPE in the mouse acetic acid-induced abdominal constriction assay. Each value represents the mean ± S.E.M. from 10 - 12 mice. Antagonist effects of nor-BNI (20 mg/kg, s.c. at -24 hr), naloxone (0.3 mg/kg, s.c. at -30 min) and NTI (3 mg/kg, s.c. at -30 min). Agonist alone, ●; +nor-BNI, ▲; +naloxone, ○ ; +NTI, △.

Table 3
ED_{50} values for TRK-820-, U-50488H-, morphine- and DPDPE-induced antinociception in the presence or absence of naloxone, nor-BNI and NTI in the abdominal constriction tests.

Agonists	Agonist alone	+nor-BNI[a)]	+naloxone[b)]	+NTI[c)]
	ED_{50} values (μg/kg, s.c.) with 95% confidence limits			
TRK-820	3.3 (2.5 - 4.3)	130 (110 - 160)*	3.5 (2.7 - 4.6)	3.4 (2.7 - 4.4)
U-50488H	1,090 (870-1,370)	16,040(13,270-19,390)*	880(660-1,190)	990 (730-1,340)
Morpnine	480 (370 -620)	510 (40 -650)	3,120 (2,340 -4,170)*	630 (500 - 780)
DPDPE[d)]	2.91 (2.18 - 3.87)	n.t.	n.t.	18.28 (11.53 - 28.99)*

a)ED_{50} values 24 h after pretreatment with 20 mg/kg, s.c. nor-BNI. b)ED_{50} values 30 min after pretreatment with 0.3 mg/kg, s.c. naloxone. c)ED_{50} values 30 min after pretreatment with 3 mg/kg, s.c. NTI. d) i.c.v. route: nmol/mouse. *Significantly different from agonist alone. ( ): 95% confidence limits. n.t. : not tested.

Interaction of TRK-820 or pentazocine with morphine on the production of antinociception

Pentazocine is an agonist to κ-opioid receptors, but is an antagonist to μ-opioid receptors. To determine if TRK-820 has pentazocine-like effect, morphine 10 mg/kg alone or in combination with TRK-820 10 or 30 μg/kg or pentazocine 3 or 10 mg/kg was injected s.c. and the antinociception was measured with high temperature hot plate test. Co-administration of TRK-820 (10 and 30 μg/kg, s.c.) with morphine slightly augmented morphine-induced antinociception. On the other hand, pentazocine significantly reduced the peak antinociceptive effect of morphine (Fig. 3). TRK-820 or pentazocine given alone at the doses used did not affect the high temperature hot plate latencies (data not shown).

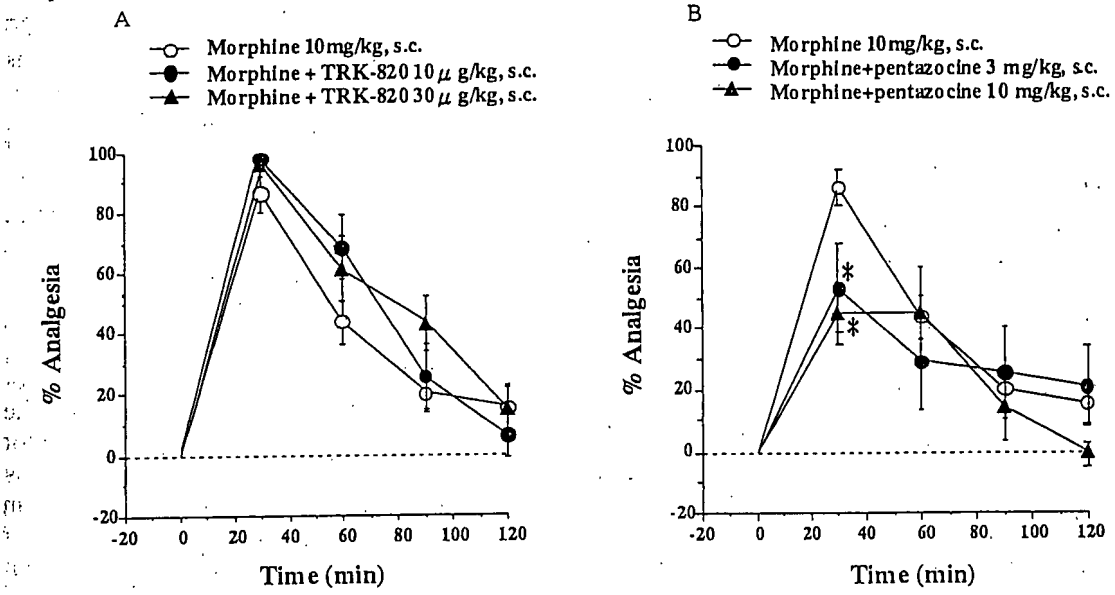

Fig. 3
Interaction of morphine with TRK-820 (A) or pentazocine (B) on the antinociceptive action in the mouse high temperature hot plate test. Each value represents the mean ± S.E.M. Ten to12 mice per group were used. * $P<0.05$ compared with morphine alone.

Table 4
Sedative effects in mouse rotarod test.

Compounds	Sedative ED_{50} values (mg/kg, s.c.)	Sedative ED_{50} /Antinociceptive ED_{50}[a)]
TRK-820	0.027 (0.020 - 0.035)	8.2
U-50488H	1.6 (1.1 - 2.1)	1.4
ICI-199441	0.0052 (0.0039 - 0.0069)	0.73
CI-977	0.031 (0.022 - 0.044)	4.5

a) ED_{50} values obtained from mice acetic acid-induced abdominal constriction test.

Rotarod test

Inhibition of rotarod performance (sedative activity) was determined by ability of mice to maintain their position on an accelerating rotarod. TRK-820 caused a dose-related inhibition of rotarod performance in mice. Other κ-opioid receptor agonists, U-50488H, ICI-199441 and CI-977, also disturbed rotarod performance in a dose-dependent manner. The ratio of the sedative ED_{50} value to the antinociceptive ED_{50} value (mouse acetic acid-induced abdominal constriction test) was found to be much greater for TRK-820 (ratio = 8.2) than those for U-50488H (ratio = 1.4) and ICI-199441 (ratio = 0.73) (Table 4).

Discussion

We recently developed a new type of κ-opioid receptor agent TRK-820 which contains 4,5-epoxymorphinan structure but not the [N-C-C-N(SP2)] pharmacophore sequence (13). TRK-820 was found to produce a potent inhibition of the electrically-evoked contractions of the mouse vas deferens (MVD) and guinea pig ileum (GPI), and showed full agonist properties. The Ke values for the opioid antagonists - naloxone, NTI and nor-BNI were 20.7 nM, 26.9 nM and 0.20 nM, respectively, in the MVD preparation, and for antagonisits-naloxone and nor-BNI were 14.5 nM and 0.052 nM, respectively, in the GPI preparation, supporting that the selective κ nature. In the present study, we clearly demonstrated for the first time in *in vivo* experiments that TRK-820 displayed potent and highly selective κ-opioid receptor agonistic actions to produce antinociception. The findings are consistent with the previous findings in *in vitro* experiments reported (13). Following systemic administration, TRK-820 produced a potent and long-lasting antinociceptive effect in various assay types of noxious stimuli including chemical, mechanical, and thermal stimuli in the mouse. On the contrary, TRK-820 was less effective in inhibiting hot plate response as compared to that of morphine. The ineffectiveness of TRK-820 to inhibit the high temperature hot plate response was consistent with its profile as a κ-opioid receptor agonist. Studies by others reported that κ-opioid receptor agonists are ineffective or less effective in inhibiting the hot plate response (17, 21). It should be noted that TRK-820 can possess a potent antinociceptive action even after p.o. administration. Other κ-opioid receptor agonists U-50488H, CI-977, ICI-199441 and PD-177302 were found to be less effective when taken orally. The results indicate that TRK-820 may be rapidly and more modestly absorbed when given by the oral route.

In terms of interaction of morphine with TRK-820 or pentazocine, co-administration of morphine with TRK-820 at doses of 10 and 30 μg/kg, s.c., which given alone did not affect the

latencies of hot plate response, slightly augmented the morphine-induced antinociceptive effect with the hot plate test. On the other hand, a mixed agonist/antagonist pentazocine at the doses of 3 and 10 mg/kg, s.c., which given alone did not affect hot-plate latencies, significantly reduced the morphine-induced hot plate inhibition These findings provide strong evidence that TRK-820 when given systematically within the antinociceptive dose range can selectively act as a agonist on κ-opioid receptors without μ-antagonistic effect.

Kappa drugs produced substantially greater sedation than other opiates and have been evaluated as anesthetic agents. TRK-820 also produced sedation at high doses, but not at the doses which produce antinociception. The therapeutic index of TRK-820, the ratio of the dose to produce sedative effects over the dose to produce antinociception, was larger than other κ-opioid receptor agonists such as U-50488H and ICI-199441. Furthermore, TRK-820 displays a lack of cross-tolerance to the U-50488-induced antinociception in mice (unpublished observation). Although more extensive studies are required, these findings suggest the possibility that TRK-820 may act on different subtypes of κ-opioid receptors (such as κ_1 or κ_3-opioid receptors).

In conclusion, TRK-820 possesses a potent antinociceptive action selectively through the activation of κ-opioid receptors without appreciable effects at μ- and δ-opioid receptors in *in vivo* experiments as well as in *in vitro* experiments.

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Links

The actions of fentanyl to inhibit drug-induced emesis.

Barnes NM, **Bunce KT**, **Naylor RJ**, **Rudd JA**.

Postgraduate Studies in Pharmacology, School of Pharmacy, University of Bradford, U.K.

The ability of fentanyl to inhibit drug-induced emesis was investigated in the ferret. Initial studies established that morphine, in small doses (0.025-0.5 mg/kg s.c.), induced emesis in the ferret that decreased at the larger doses of 1 and 2 mg/kg (s.c.). Fentanyl (10-80 micrograms/kg s.c.) failed to induce emesis but in this dose range prevented the emesis induced by morphine (0.5 mg/kg s.c.), apomorphine (0.25 mg/kg s.c.), copper sulphate (100 mg/kg intragastric) and cisplatin (10 mg/kg i.v.). The antiemetic effects could be obtained in the absence of sedation or motor impairment. The antagonism by fentanyl of apomorphine-, copper sulphate- and cisplatin-induced emesis was inhibited by naloxone (0.1 or 0.5 mg/kg s.c.). It is concluded that fentanyl exerts a broad spectrum of actions to inhibit drug-induced emesis. An autoradiographic study of the binding of [3H]DAGO to the brainstem of the ferret indicated high densities of mu recognition sites in the area postrema, nucleus tractus solitarius, dorsal motor nucleus of the vagus, reticular medulla and other sites. The results are discussed in terms of balanced facilitatory and inhibitory opioid systems, regulating emesis and that the antiemetic actions of fentanyl reflect an important, although not necessarily an exclusive, action at mu opioid receptors.

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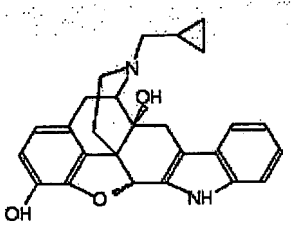

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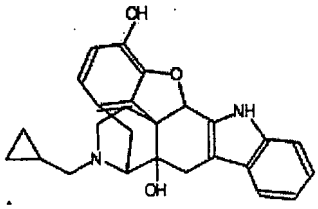

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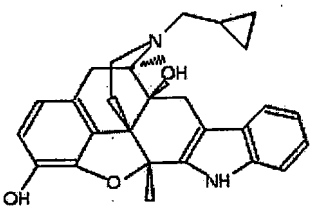

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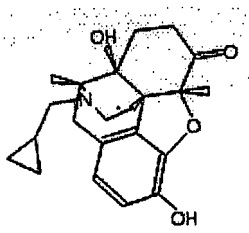

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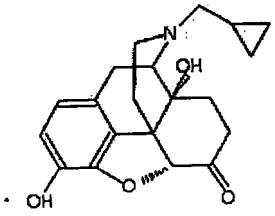

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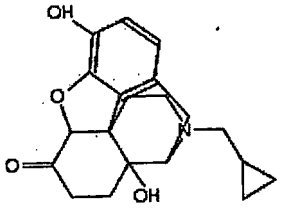

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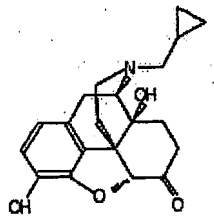

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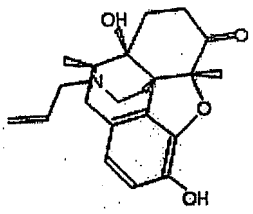

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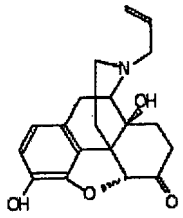

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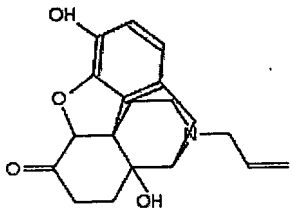

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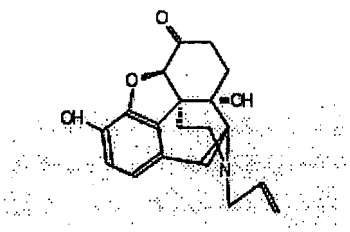

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